Family Aggregation of Pulmonary Function Measurements[1-3]

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SUMMARY Family aggregation of pulmonary function measurements was analyzed in the nuclear families of the Tucson epidemiologic study of airway obstructive diseases (AOD). There were 271 parental pairs and their natural children who had satisfactory pulmonary function data. Initial regression analysis showed significant correlations of the pulmonary function variables after controlling for age and sex. Body habitus, as measured by the Ponderal index, was highly aggregated as well. Pulmonary function measurements were aggregated in families independent of family size, reported diagnosed AOD, and children's smoking, even though both asthma and smoking showed significant familial aggregation. After controlling for the familial aggregation of body habitus, a major determinant of pulmonary function, there was no remaining independent aggregation of pulmonary function measurements. It was also determined that parental passive smoking had no effect on children's pulmonary function measurements.

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Introduction

Clinicians have noted that airways obstructive diseases, especially emphysema, appear to run in families, and this has been a common observation since the early nineteenth century (1, 2). Except for the rare homozygotic alpha$_1$-antitrypsin deficiency, other genetic predispositions to chronic obstructive diseases have not been clearly demonstrated (3). Studies in England have demonstrated that there is a genetic basis of asthma (4, 5). Recent studies have demonstrated aggregation of pulmonary function in twins (6, 7), and recent population studies have shown that pulmonary function measurements appear to be aggregated in families (8-10).

It has long been recognized that body size and configuration are genetically determined, yielding familial aggregation of body habitus; body habitus has a major influence on pulmonary function. Although adjustment for height to predict a person's lung function is standard, this is not sufficient when examining interindividual correlations of body habitus with lung function. Thus, it is necessary to evaluate the interaction of body habitus in the analysis of familial aggregation of pulmonary function.

This report attempts to examine the relationship of pulmonary function measurements in the family, of body habitus relationships in the family, and the interaction thereof. The influence of a history of airways obstructive disease in parents and children, smoking in parents and children, family size, and the influence of passive smoking, which are possible confounding variables, are examined as well.

Methods

Data on nuclear families reported herein are derived from the Tucson Epidemiological Studies of Airways Obstructive Diseases, which has been described previously (11). The population under study is a multistage stratified cluster sample of white, non-Mexican-American families in the Tucson area, where stratification was on age of head of household and on socioeconomic status.

In the first year of this study (1972-1973), questionnaires were completed on all subjects. These included a respiratory history and a family history with a family tree. Subjects 12 yr of age and older completed their own questionnaires. Mothers, or substitutes if the mothers were not available, completed them for children younger than 12 yr of age (11). Comparisons of maternal and self reporting performed for smoking histories showed no discrepancies. A separate study showed no significant differences, in children 8 to 11, in parental versus self reporting of chronic symptoms (12). Pulmonary function tests were performed satisfactorily in over 90% of those 6 yr of age and older, using techniques previously described (13).

Nuclear families were defined as families in which there were a mother, a father, and at least one natural child of the pair. There were 344 nuclear families of the 1,655 families studied (approximately 25%). The number of subjects involved in these nuclear families represent about 1,400 of the 3,800 subjects in the total study population. There were 271 families in which both parents and 1 or more of their children had satisfactory pulmonary function measurements in the first year of the study. These were analyzed as units. We also considered relationships between parent-child pairs, spouse pairs, and sibling pairs.

The presence of airway obstructive disease in the children and the parent was obtained from the questionnaires, as was smoking history (for those 15 yr of age and older). Family size, obtained from household records, was also used to determine if it was a confounding variable.

As previously described, all measurements were made by trained nurse interviewers; tests of interobserver variability i all measurements indicated no significa differences (11, 13). Standing height (H) i inches, sitting height in inches, and weig (W) in pounds were used to calculate t Ponderal Index (14), an index of body hab tus (i.e., $H/\sqrt[3]{W}$). This index had the be correlation with pulmonary function tes when compared with other indexes of bo habitus.

The pulmonary function measuremen used were: forced vital capacity (FVC forced expiratory volume in one seco (FEV_1), and maximal expiratory flows aft 50 and 75% of the FVC had been expir ($\dot{V}max_{50}$ and $\dot{V}max_{75}$, respectively). Ea subject's function was first corrected f height and weight, using regression equ tions derived from data on asymptoma nonsmokers in this population. These c rected values did not explain all effects body habitus.

Comparisons of children's and paren pulmonary function variables (expressed percent predicted) were performed fir before accounting for parental body ha tus; these were performed before and af Z-score transformations. The Z-scores standard normal variates: for each subje the observed value was subtracted from

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group mean and divided by the group standard deviation ($z_i = (x_{ijk} - \bar{x}.jk)/s.jk$, for each i subject, j age group, k sex). This removed further effects of age and sex and gave all values the same units. All pulmonary function variables were then adjusted for the individual child's Ponderal Index and the parental Ponderal Indexes (where significantly correlated with the pulmonary function variables) using regression techniques. The Z-scores were recalculated for each of these pulmonary function variables within each age-sex group represented in the parent-child pairs. The Z-score technique is useful for looking at specific effects of other explanatory variables, such as smoking.

Familial aggregation was estimated by analysis of variance (ANOVA), which corresponds to the intraclass correlation as described by Donner and Koval (15). These investigators demonstrated that this method was slightly better than the maximal likelihood estimator if the true correlation was likely to be less than 0.5. Both were better than the usual product-moment correlation method. They also demonstrated that differences in results with inclusion or exclusion of one child were minimal and nonsignificant. The multivariate components of variance method of ANOVA is more useful than other methods of examining aggregation in that it gives separate estimators for variance components and allows usual testing of significance of those estimates. Analyses of variance were performed using the children's pulmonary function measurements as the dependent variable, using age, sex, smoking, and body habitus indexes of the children and the parents as covariates, with parents' pulmonary function (as continuous variables) as the explanatory variables (main effects) in the ANOVA. Covariates were all continuous variables except sex. Main effects were grouped into equal thirds. Two- and three-way interactions were examined. The regression option was used to remove covariate effects, other main effects, and interaction effects from the contribution of each main factor, using SPSS programs on a DEC-10 Cyber 175 University Computer System. In the case of nuclear family analyses using analyses of variance, the analyses were done for all families and separately and for those with 2 or more children (13). For analysis of parent-child pairs, the male/female oldest child was used. For analysis of sibling pairs, the 2 oldest children of each sex in the family were used.

Results

The characteristics of members of the nuclear families with pulmonary function tests are shown in table 1. There were highly significant product-moment correlations of measures of body habitus between all children and their parents, after adjusting for age and sex.

TABLE 1

CHARACTERISTICS OF PARENTS AND CHILDREN (8 YEARS OF AGE AND OLDER) IN NUCLEAR FAMILIES WITH PULMONARY FUNCTION

	Children (n = 354)		Mothers (n = 278)		Fathers (n = 268)	
Characteristics	Mean	SD	Mean	SD	Mean	SD
Age	13.5	5.0	38.1	8.8	39.4	12.2
Height (H) (in.)	60.8	7.5	63.9	2.3	69.3	2.5
Weight (W) (lb.)	106.4	41.0	134.9	24.8	172.5	24.8
$H/W^{1/3}$	13.1	0.8	12.5	0.7	12.5	0.5
%FVC	110.3	23.9	102.3	16.5	101.2	15.0
%FEV_1	106.5	21.3	104.8	18.9	104.2	17.5
Eversmokers, %	1.7*		80.0		72.3	

Definition of abbreviations: %FVC = percent predicted forced vital capacity; %FEV_1 = percent predicted forced expiratory volume in one second.

* n = 181, 18 yr of age and older only.

The linear regression of all the children's $H/W^{1/3}$ on mothers' $H/W^{1/3}$ had a correlation (r) of 0.804 ($p < 0.0001$); with fathers, r was 0.773 ($p < 0.0001$). There were also some significant product-moment correlations of the amount of smoking (pack-years) between various pairs, especially between fathers and children siblings and spouses ($p < 0.001$), even though many fewer children than parents smoke. The significant correlations were between father and both daughters and sons, between siblings, and between spouses; the mothers-sons correlation of smoking was borderline ($p = 0.085$). There was no correlation of smoking with any of the measurements of body size or habitus.

Product-moment correlations between children's and parents' pulmonary function measurements were statistically significant (r as much as 0.30) prior to adjusting for covariates. The most significant aggregation of a pulmonary function measurement prior to body habitus correction was with FVC, which as a volume measurement is most closely correlated with body habitus. The relationships were also strong and significant for FEV_1, but were less often significant for the flow variables. However, regressions of the children's percent predicted pulmonary function against parents' pulmonary function and body habitus measurements showed significant correlations of the children's pulmonary function with the parents' body habitus, as well as with their own body habitus. After body habitus and age corrections, the previous correlations of pulmonary function variables between any of the pairs were no longer present. Thus, the relation between children's lung function and parents' lung function is likely to be related to their similar body habitus.

Despite the aggregation of asthma (table 2), it was not a factor in the aggregation of pulmonary function measurements when tested by ANOVA. There was no family aggregation of present diagnosed chronic bronchitis for emphysema. The presence of these other airway obstructive diseases in parents and/or children were not factors in the relationships between pulmonary function measurements in the family (by ANOVA). Family size was not found to be a significant factor in any of the analyses. Analyses of variance for families with 2 or more children only, as well as for all families (1 child or more), yielded similar results.

TABLE 2

PHYSICIAN-CONFIRMED EVER ASTHMA IN NUCLEAR FAMILIES

	No Asthma in Parents	One Parent with Asthma	Both Parents With Asthma
Families, n	273	66	3
Families with 1+ asthmatic child, %	10.6*	28.5	100
Oldest children with asthma, %	8.5	19.1	33.3
Children, n	538	122	11
Children with asthma, %	6.5*	18.7	63.6

* Rates of asthma significantly higher with one or more asthmatic parents ($p < 0.005$).

TABLE 3

CHILDREN'S VOLUME AND FLOW MEASUREMENTS IN RELATION TO PARENTS' VOLUME AND FLOW MEASUREMENTS, CONTROLLING FOR OTHER VARIABLES (BY ANOVA)*

		FVC			$\dot{V}max_{50}$		
	df†	Mean Square	F	p	Mean Square	F	p
No controls							
Father's function	2	3,096.1	8.67	0.001	1,837.5	2.57	0.078
Mother's function	2	2,348.4	4.84	0.008	1,551.8	2.44	0.088
Interaction	4	319.9	0.89	0.600	417.1	0.66	0.624
Explained	8	1,756.2	3.78	0.001	977.4	1.54	0.145
Age, sex, and smoking controls							
Covariates‡	6	4,196.3	10.89	0.001	2,742.5	4.88	0.001
Father's function	2	919.8	2.39	0.094	1,031.3	1.76	0.174
Mother's function	2	1,369.2	3.55	0.030	1,475.8	2.52	0.083
Father's smoking	2	268.8	0.70	0.499	1,366.5	2.33	0.099
Mother's smoking	2	42.8	0.11	0.895	1,128.6	1.93	0.148
2-way interactions§	24	482.3	1.25	0.196	663.1	0.98	0.519
Explained	37	1,276.2	3.31	0.001	1,052.1	1.80	0.005
Age, sex, and habitus controls,‖ adjusted children's function¶							
Covariates‡	4	1,462.8	5.72	0.001	1,831.6	2.55	0.040
Father's function	2	511.4	2.00	0.138	408.1	0.64	0.529
Mother's function	2	274.9	1.08	0.343	88.1	0.14	0.874
2-way interactions	24	487.9	1.91	0.009	944.8	1.48	0.078
3-way interactions	32	382.1	1.49	0.052	420.4	0.66	0.921
Explained	66	623.4	2.44	0.001	770.5	1.21	0.163

Definition of abbreviations: df = degrees of freedom; FVC = forced vital capacity; $\dot{V}max_{50}$ = maximal flow after exhalation of 50% of FVC; F = variance ratio.

* "Regression option" (see text).

† Total = 287 without habitus controls, less with habitus data, as complete data missing from 1 or more members of some families.

‡ Parents' habitus also as main effects.

§ No three-way interactions.

‖ Children's function adjusted for their and parents' body habitus (using the Ponderal index).

¶ All ages, children's sex and smoking/habitus.

To account for all of the possible significant covariables and interactions, we used multivariate analysis of variance to evaluate aggregation of FVC, FEV_1, $\dot{V}max_{50}$, $\dot{V}max_{75}$. Each explanatory variable was treated as an independent contributor to the dependent variable. The results for all 4 pulmonary function variables were similar, so only 1 volume (FVC) and 1 flow ($\dot{V}max_{50}$) variable are shown (table 3).

Without covariate controls or adjusted children's pulmonary function, the parents' volume measurements contributed significantly to the explanation of the children's measurements. These significant relationships for FVC, FEV_1, and $\dot{V}max_{50}$ were also present after age and sex were used as covariates and parental smoking was used as explanatory variables (table 3). However, adjusting for smoking reduced the significance of fathers' FVC and both parents' $\dot{V}max_{50}$. Parents' smoking was significant only for $\dot{V}max_{75}$ (maternal smoking only). Furthermore, we did not find any relation between fathers' or mothers' smoking and their spouses' pulmonary function.

The body habitus-corrected FVC and $\dot{V}max_{50}$ of the children as the dependent variables had no significant relationship with any of the explanatory variables, where both the parents' pulmonary function variables had been corrected for body habitus as well. The total amount of variability explained in these analyses was significant for FVC and FEV_1 ($p = 0.001$).

The analyses of variance performed on the pulmonary function measurements of parent-oldest child, spouse, or sibling pairs yielded negative results. There were two exceptions to this: the contribution of the father's $\dot{V}max_{50}$ on the daughter's $\dot{V}max_{50}$ was significant ($p = 0.046$); however, the total variance explained was not significant. As that only left 1 of 24 comparisons significant, mother-son FVC (p of main effect = 0.028), and one might expect approximately 1 of these many comparisons ($n = 24$) to be significant by chance alone (at $p \leq 0.05$), this was considered a chance finding. Performing the same analyses after correcting for smoking habits in the parents and children, and after analyzing by whether airways obstructive diseases were present or not, did not change the results.

The children's Z-score-corrected pulmonary function variables were compared among smoking and nonsmoking parents; the results are shown in table 4. As can be seen, parental smoking did not have a significant effect on children's pulmonary function; smoking habits of others in the household (predominantly siblings) did not have any effect either.

Discussion

It is generally agreed that body habitus is genetically determined; it certainly has high familial aggregation. Pulmonary function variables are measurements that are highly dependent on various characteristics of body habitus. Pulmonary function measurements have previously been shown to aggregate in families when body habitus in the families was not accounted for (8, 9). In our study, we first saw strong correlations between parents' and children's pulmonary function measurements, significant for FVC, FEV_1, and $\dot{V}max_{50}$. However, when we controlled for body habitus in the examination of the relationship between parents' and

TABLE 4

Z VALUES OF CHILDREN'S PULMONARY FUNCTION BY PARENTAL SMOKING

		FVC		FEV_1		$\dot{V}max_{50}$		$\dot{V}max_{75}$	
Parental Smoking	n	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Neither	48	−0.08	1.00	−0.12	0.99	−0.16	1.19	−0.08	1.06
Mother smokes	36	−0.16	0.93	−0.16	0.81	−0.15	0.85	0.0	0.89
Father smokes	82	−0.06	0.91	−0.04	0.97	−0.17	0.95	−0.17	1.01
Both smoke	96	+0.19	1.08	+0.23	1.06	+0.15	0.99	+0.20	0.97
Total	271	0.01	0.99	0.03	1.00	0.0	1.00	0.0	1.00
	df	Mean Square		Mean Square		Mean Square		Mean Square	
Between	3	1.578		2.212		1.386		2.314	
Within	267	0.987		0.975		0.992		0.982	
F		1.632		2.269		1.396		2.356	
p		0.182		0.081		0.244		0.072	

For definition of abbreviations, see table 3.

children's pulmonary function measurements, we no longer found such relationships. Thus, familial correlations for observed pulmonary function, especially FVC, were dependent on familial aggregation of body habitus, even after controlling for age and sex. It can not be construed as an overadjustment of familial data, as the underlying familial aggregation is one of body habitus characteristics. This is more a genetic effect than one of dietary or environmental effect, as shown by the weaker relationship between siblings and the lack of a relationship of body habitus between spouses.

On the other hand, we did detect a familial relationship of asthma between children and parents independent of smoking and pulmonary function measures (table 2), which confirmed findings of Sibbald and coworkers (4, 5), and Townley and associates (16). To insure that this is not strictly a result of reporting bias, objective measures such as bronchial-reactivity would have to be done to confirm the relationship, as has been done by Townley and associates (16). This familial aggregation of asthma did not affect the findings for any familial aggregation of pulmonary function.

We found also that smoking habitus aggregated in families but was probably an environmental influence only. Spouses and siblings had the closest relationships of smoking habits (r = 0.29 and 0.50, respectively). Smoking habits of both sons and daughters correlated more highly with those of their fathers (r = 0.22 and 0.23, respectively) than with those of their mothers (r = 0.08 and 0.03, respectively).

Previously, we had not found a relationship between children's and parents' chronic symptoms by parental smoking (20). When we examined effects of parental smoking on children's pulmonary function, taking into account the initial relationship between parental and children's pulmonary function, only maternal smoking was a significant explanatory variable, and only for $\dot{V}_{max_{50}}$ (p = 0.043). Considering the number of ways in which the comparisons were made, this one difference probably was not meaningful. When children's pulmonary function was adjusted for paternal body habitus as well as their own, there was no significant parental smoking contribution. A lack of a relationship between parental smoking and children's pulmonary function, even without correcting for parental pulmonary function or body habitus, had been reported by Speizer and coworkers (17, 18), Schilling and associates (10), and Dodge (12). Tager and colleagues (19) had reported this association, but it too might disappear if corrected for the family aggregation they found (9), and/or body habitus. It is possible that controlling for body habitus in a family may be controlling for other genetic and host factors as well.

Finally, we did not find any significant interaction between the smoking habits of either parent smoking and their spouses' lung function (table 3), similar to Comstock and coworkers (21) and Schilling and associates (10), but different from Kauffmann and coworkers (22).

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